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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,045	01/23/2002	Rose-Mary N Boustany	5405.225	9439
20792	7590	12/30/2005	EXAMINER	
MYERS BIGEL SIBLEY & SAJOVEC PO BOX 37428 RALEIGH, NC 27627				GOLDBERG, JEANINE ANNE
		ART UNIT		PAPER NUMBER
				1634

DATE MAILED: 12/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/830,045	BOUSTANY ET AL.	
	Examiner	Art Unit	
	Jeanine A. Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 23 November 2005.
 2a) This action is FINAL. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-6 and 8-10 is/are pending in the application.
 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 1-6 and 8-10 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
 Paper No(s)/Mail Date _____

4) Interview Summary (PTO-413)
 Paper No(s)/Mail Date. _____.
 5) Notice of Informal Patent Application (PTO-152)
 6) Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed November 23, 2005. Currently, claims 1-6, 8-10, are pending.
2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 23, 2005 has been entered.
3. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.
4. Any objections and rejections not reiterated below are hereby withdrawn in view of the amendments to the claims or applicant's remarks.

Priority

5. This application is a 371 of PCT/US99/24695, filed October 21, 1999 which claims priority to provisional application 60/105,262, filed October 22, 1998.

Drawings

6. The drawings are acceptable.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-6, 8-10, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 1-6, 8-10, are broadly drawn to methods of identifying a human subject having an increased risk of developing breast or colon cancer by detecting the upregulation of "the CLN3 gene" wherein the upregulation of the CLN3 gene in the subject is indicative of an increased risk of developing breast cancer or colon cancer.

The claims further require upregulation of "the CLN3 gene." The specification teaches that the CLN3 gene referred to herein is known, and is also referred to as the

Batten Disease gene. Further the claims are not limited to any particular CLN3 gene by either species or structure (i.e. SEQ ID NO:).

The teachings of the specification and working examples

The specification teaches an analysis of breast cancer cell lines, colon cancer cell lines (Figure 9-12, page 7-8), melanoma cell lines, neuroblastoma cell line, glioma cell line and glioblastoma cell line. The specification teaches that the melanoma cell lines actually had "less CLN3 expressed" (page 8, lines 15-18). Each of these analyses was performed on cell lines. The specification fails to provide any evidence that a similar pattern of over-expression is present in actual tumor tissue. There is no evidence that the correlation between upregulation of CLN3 would be present in actual tissues. Moreover, in the analysis provided, not all of the cell lines were correlated in the same manner with CLN3 expression. The over-expression of CLN3 in cancer cell lines is not sufficient evidence to enable one skilled in the art to determine that this nucleic acid would necessarily be over-expressed in primary tumor tissue as compared to non-tumor tissue.

The specification has no working examples of solid tumors in a representative number of proliferative disorders, as defined by the instant specification. While there are cell line examples for human cancers, there are no tissue working examples for solid tumors in human.

The unpredictability of the art and the state of the prior art

There is a great deal of unpredictability in the expression of nucleic acids as indicative of diseases. As noted by the instant specification, not every cell line acts in a concordant manner, see the melanoma cell line, for example.

Moreover, Dermer *et al.* (Biotechnology Vol. 12, March 1994, p. 320) teach that cell lines are a poor representation of malignancy because they have survived crisis and have adapted an immortal life in culture, and thus has been enabled to survive in its artificial environment. Dermer *et al.* state that "the petri dish cancer is really a poor representation of malignancy, with characteristics profoundly different from the human disease."

With regard to a specific nucleic acid, namely PARP, Chabert *et al.* (Int. J. Cancer: 53, 837-842 (1993)) compare PARP gene expression, enzymatic activity and quantities in 3 animal tumor cell lines in culture verses those transplanted into a compatible host, and found that, for "a given tumor cell line, marked differences exist in poly(ADPR)P gene expression and enzymatic activity between cultured cells and cells obtained from solid or ascitic tumors. Indeed, poly(ADPR)P gene expression, endogenous activity and amount are higher in exponentially growing cells than in *in vivo* tumors (p. 837, see also Fig. 1)." Chabert *et al.* further suggest that such discrepancies in enzymatic activity between cell culture and *in vivo* growth conditions exist because of differences in proliferation rates and/or environmental conditions (p. 841). Thus, before determining that a certain cell line is associated with a proliferative disease, the skilled artisan would be required to perform experiments to ensure there is a correlation.

The post filing date art further confirms the unpredictability of this area. Rylova *et al.* (Cancer Research, Vol. 62, pages 801-808, February 1, 2002) teaches that CLN3 mRNA is not overexpressed in either melanoma or pancreas cell lines (see Figure 1, page 803).

Further, Persaud-Swawin (Hum. Mol. Genetics. Vol. 11, No. 18, pages 2129-2142, 2002) teaches there are many mutations in CLN3 including a 1.02kb deletion which causes a truncation due to the loss of amino acids 54-438. Persaud-Swawin also

teaches that homologs for CLN3 in the dog, mouse, *Caenorhabditis elegans* and yeast bear 78%, 75%, 37%, and 34% identity to the human CLN3 gene, respectively. Thus, it is unclear which “CLN3” gene is required by the instant claims and further whether each CLN3 is enabled for detecting tumors.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to apply this association to solid tumors from individuals rather than cell lines and to each of the claimed proliferative diseases.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Guidance in the Specification.

The teachings of the specification do not establish that one could actually detect upregulation or overexpression of CLN3 as an indicator of proliferative diseases in general, let alone in any each of the claimed proliferative disorders in any species including but not limited to dogs, cat and horses. Rather the teachings of the specification asserts that CLN3 is expressed at higher levels in several cell lines, but not differentially expressed in other cell lines. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. While one could conduct additional experimentation to determine whether, e.g., expression of CLN3 might be associated with e.g., the specifically claimed proliferative disease, the outcome of such research

cannot be predicted, and such further research and experimentation are both unpredictable and undue.

It is recognized that the specification, the claims and the arguments intend for the invention to encompass any species and any CLN3 gene. It is not clear what is encompassed by "the CLN3 gene." The art teaches numerous sequences, mutations and truncations of the CLN3 gene. The specification does not specifically teach which "CLN3 gene" is required. The art teaches that homologs for CLN3 in the dog, mouse, *Caenorhabditis elegans* and yeast bear 78%, 75%, 37%, and 34% identity to the human CLN3 gene, respectively. It is unpredictable which CLN3 gene is required and which CLN3 genes would be overexpressed as indicative of particular proliferative diseases. Moreover, it is unpredictable that the CLN3 gene overexpression is essential for all subjects including the mouse and dog for example. The specification does not appear to provide any guidance in the specification that the CLN3 gene in dogs is overexpressed in breast cancer, for example. While one could perform experimentation on the dog gene, it is unpredictable that CLN3 is associated with overexpression in cancer without unpredictable experimentation.

The specification merely discloses upregulation of CLN3 in a few cell lines, not all cell lines, which are asserted to be cancer models. While the ordinary practitioner in this field is highly skilled, the evidence presented in the specification does not provide even a highly skilled practitioner means to overcome the limitations of evidence derived from cell lines and to make and/or use CLN3 as a method for cancer diagnosis and/or detection with any reliability. As discussed by Dermer *et al.* and Chabert *et al.* the level of predictability between the activity of tumor cell lines and actual tumor tissue is very low, and thus practicing this invention would require unreasonable experimentation on

the part of the practitioner to further screen actual tumor tissue to test for a connection between CLN3 over-expression and cancer.

However, as noted above, cell lines are not sufficient models for cancer. In the absence of guidance from the specification, one skill in the art may look to the teachings of the prior art for enablement of the claimed invention. However, the closest prior art does not provide support for the use of CLN3 expression as an indicator for all proliferative diseases, including cancers, asthma, arthritis, fibrosis etc. Thus, it is unpredictable as to whether one could successfully use the claimed invention, and given the fact that neither the specification nor the prior art provide evidence of a correlation or association between CLN3 expression and proliferative disease, it is further unpredictable as to whether any quantity of experimentation would allow one to practice the claimed invention. Accordingly, it would require undue experimentation for a skilled artisan to use the claimed invention. In light of the teachings in the prior art, and the general unpredictability concerning the activity of CLN3 in tumor cell lines versus actual tumor tissue, the specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the presence of a possible association between CLN3 in cancerous cell lines for humans, the factor of unpredictability weighs heavily in favor of undue experimentation. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized problems in the use of the cell lines. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define an association for screening a subject, the lack of

guidance provided in the specification, and the absence of a working examples directed at subjects balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The response traverses the rejection.

The response asserts that the claims are enabled by data provided in the specification in Example 2 (pages 25-28). This argument has been thoroughly reviewed, but is not found persuasive because Example 2 is drawn to human cell lines. As discussed at length above, the cell lines of the instant specification are not indicative or representative of solid tumors in human subjects, as claimed in the instant claims.

The experimentation required to use data from cell lines in human analysis is unpredictable given the state of the art of predicting tumors in tissue based upon cell lines, as argued above.

The previous response asserted that cell lines are in fact a sufficient model for the claimed invention. This argument has been reviewed but is not convincing because the objective evidence of record does not support this assertion made by applicant's attorney. MPEP 716.01(c) makes clear that "The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long - felt need, inoperability of

the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant." Here, the statements regarding the sufficiency of cancer cell lines for the claimed invention must be supported by evidence, not argument. The objective evidence of Dermer and Chabert each teach that cell lines and tumors show marked differences in expression.

The response asserts that CLN3 sequence is highly conserved across species and submits that Rylova (a post filing date piece of art by the inventors) supports this assertion for colon tissue. Rylova is silent on the issue of breast cancer. This argument has been thoroughly reviewed, but is not found persuasive because the Rylova article is post filing date art. In the response applicants submitted a post filing date reference from the inventors of the instant application and that the filing of such a reference does not provide objective evidence of enablement of CLN3 overexpression in human. As provided in MPEP 2164.05(a) "Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. *In re Gunn*, 537 F.2d 1123, 1128, 190 USPQ 402,405-06 (CCPA 1976); *In re Budnick*, 537 F.2d 535, 538, 190 USPQ 422, 424 (CCPA 1976) (In general, if an applicant seeks to use a patent to prove the state of the art for the purpose of the enablement requirement, the patent must have an issue date earlier than the effective filing date of the application.). While a later dated publication cannot supplement an insufficient disclosure in a prior dated application to make it enabling, applicant can offer the testimony of an expert based on the publication as

evidence of the level of skill in the art at the time the application was filed. Gould v. Quigg, 822 F.2d 1074, 1077, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987)."

Moreover, as provided in 716.02(g) "The reason for requiring evidence in declaration or affidavit form is to obtain the assurances that any statements or representations made are correct, as provided by 35 U.S.C. 25 and 18 U.S.C. 1001." Permitting a publication to substitute for expert testimony would circumvent the guarantees built into the statute. Ex parte Gray, 10 USPQ2d 1922, 1928 (Bd. Pat. App. & Inter. 1989). Further, the instant publication was published approximately 3 ½ years after the filing date of the instant application. Moreover, even if human colon tumors were found to be enabled in 2002, there is no evidence that CLN3 genes were known to be overexpressed in breast tumors.

The response asserts that the articles used to support the enablement rejection are not specifically drawn to CLN3 and breast/colon cancer. This argument has been thoroughly reviewed, but is not found persuasive because the art provided illustrates that it is unpredictable whether or not cell lines are acceptable models. The art teaches numerous examples of incidences where cell lines and tumor samples are not correlative. It is unpredictable whether the cell lines of the instant application and solid tumors are correlative absent further experimentation.

The response also addresses the Dermer article and states that Mr. Dermer is a cancer researcher, but no other credentials are provided that establish Mr. Dermer as one of appropriate skill in the art to speak on the issue of cell lines. This argument has been thoroughly reviewed, but is not found persuasive the article by Dermer has been

used to illustrate the unpredictability in the art. While the credentials of Dr. Dermer are not relevant to the unpredictability in the art, an internet search of Dr. Gerald B. Dermer yielded his credentials.

Dr. Gerald B. Dermer received his B.A. in biophysics, M.A. in genetics, and Ph.D. in cell biology from the University of California at Los Angeles. After two years of post-doctoral research in biochemistry at the University of Lund in Sweden, Dr. Dermer returned to Los Angeles and the Pathology Department of the Hospital of the Good Samaritan. There he began his research on human cancer, joining the faculty of the University of Southern California School of Medicine.

After twelve successful years in clinical and basic research, Dr. Dermer moved to the University of North Carolina School of Medicine, where he continued laboratory research for three more years. For the past ten years, Dr. Dermer has pursued his interests in cancer, pathology, and biotechnology as an independent consultant and writer.

Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

8. No claims allowable.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272- 0745.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.


Jeanine Goldberg
Primary Examiner
December 27, 2005